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Surgery Section

Effectiveness of Centchroman on Regression of Fibroadenosis and Mastalgia

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ABSTRACT

Introduction: Fibroadenosis and mastalgia are common among the women in reproductive age group. Treatment for these conditions is not yet standardised. Most of the drugs used for fibroadenosis and mastalgia are expensive and have side effects.

Aim: To find out the efficacy of centchroman, a Selective Estrogens Receptor Modulator (SERM) on regression of fibroadenosis and mastalgia.

Materials and Methods: Fifty one patients with mastalgia/fibroadenosis were treated with centchroman 30mg once daily on alternate days for a period of 3 months and followed up weekly for six months with Mastalgia chart and Visual Analog Scale (VAS) pain score.

Results: Before starting treatment, four patients presented with pain score of 6 followed by, 37 patients with a score of 4 and 10 patients with a score of 2. All the patients were started on tab centchroman 30mg OD alternate days and were reviewed on weekly basis with Mastalgia chart and VAS pain score for three months. On fifth and sixth visit, 46 patients reported with pain score 0, one with pain score of 2 and four with pain score of 6. The efficacy of centchroman was found to be significant (p-value = 0.001). Three patients (5.9%) reported epigastric pain and ten patients (19.6%) reported menstrual delay. A total of 38 patients did not complain of any side effect.

Conclusion: Our study proves that centchroman is a safe and cost effective drug with significant efficacy on regression of fibroadenosis and mastalgia with minimal side effect.

Keywords: Cyclical, Fibroadenoma, Fibrocystic disease, Hormonal therapy, Non-cyclical, Ormeloxifene

INTRODUCTION

Breast pain among women, with or without lump is common complaint and a cause of significant anxiety and fear of breast cancer [1]. Annually 200,000 breast disorders are identified [2] and it is noted that most of the palpable lesions are benign [3]. Approximately half of the women in reproductive age group suffer from Benign Breast Diseases (BBD) [4-11]. Among the BBD, mastalgia, fibrocystic disease and fibroadenoma are the most common. Mastalgia (Greek masto-breast and algia-pain) signifies breast pain. It can be classified into two types:

1) Cyclic mastalgia: Characterized by more pain during the menstrual cycle and it is frequently related with fibrocystic breast changes or duct ectasia. Minimal tenderness during menstrual cycle is thought to be typical, and is normally associated with menstrual cycle and/or premenstrual syndrome (PMS) [12-14].

2) Non-cyclic mastalgia: Characterized by the pain, which is unaltered during the menstrual cycle. This type is not common. It has different causes and difficult to diagnose. Non- cyclical pain is not usually related with the menstrual cycle. Some level of non-cyclic breast tenderness is present because of hormonal changes in adolescence, pregnancy and menopause [12-14].

Breastfeeding is additionally one of the reasons for non-cyclic pain. Fibrocystic breast disease is otherwise called Fibroadenosis. It is a non-carcinogenic breast condition, which presents as a diffuse lump and is connected with hormonal changes (menstrual cycle) [12-16]. Many women experience the ill effects of fibrocystic disease particularly in their conceptive age. Fibrocystic diseases are uncommon among menopausal women. Fibrocystic changes can happen in one or both breasts. A post mortem study conducted in 2005 by Courtillot C et al., concluded that 50% women had some form of fibrocystic disease and 20% had fibroadenoma [14].

Most of the drugs used for fibroadenosis and mastalgia are expensive and have side effects. Till date, only four articles are available in medical literature on Centchroman for regression of fibroadenosis and ours is fifth one. Multicentre randomised double blind controlled studies with larger sample size in comparison with other drugs are needed for global acceptance. This study was conducted to find out the efficacy of centchroman, a Selective Estrogens Receptor Modulator (SERM) on regression of fibroadenosis and mastalgia.

AIM

To study the effectiveness of centchroman (ormeloxifene) on regression of fibroadenosis and mastalgia and to evaluate its side effects.

MATERIALS AND METHODS

This non-randomised prospective study was conducted in General Surgery Department of our medical college hospital, Pondicherry after institutional ethics committee approval from July 2013 to July 2015. Fifty one female patients presented with complaints of breast pain or swelling in the breast were included in the study. Diagnosis of fibroadenosis was made by ultrasound guided Fine Needle Aspiration Cytology (FNAC) and mastalgia by history. For all patients ultrasonography of abdomen was done to rule out ovarian diseases and uterine cervical hyperplasia. Patients fulfilling inclusion criteria were explained in detail about the study and were started on Tab. Centchroman 30 mg alternate days for a period of 3 months. Patients were taught how to mark mastalgia chart. Patients were reviewed in General Surgery outpatient department every month with the marked mastalgia chart. Patients were followed up to 6 months and the results were recorded as per clinical examination, Visual Analog Scale (VAS) for pain. Results were compared using t-test and p-value was calculated.

Exclusion criteria

- Patients who are pregnant, lactating women and who are planning to have pregnancy in near future.

- Patients who have history of breast carcinoma or family history of breast carcinoma.
- Patients with polycystic ovarian diseases and uterine cervical hyperplasia.
- Patients diagnosed to have associated chest wall disorder and dermatological lesions.

STATISTICAL ANALYSIS

All data was entered into a Data Collection Proforma Sheet and were entered into MS Excel 2011. Statistical analysis was carried out using SPSS version 19.0 software with Regression Modules installed.

RESULTS

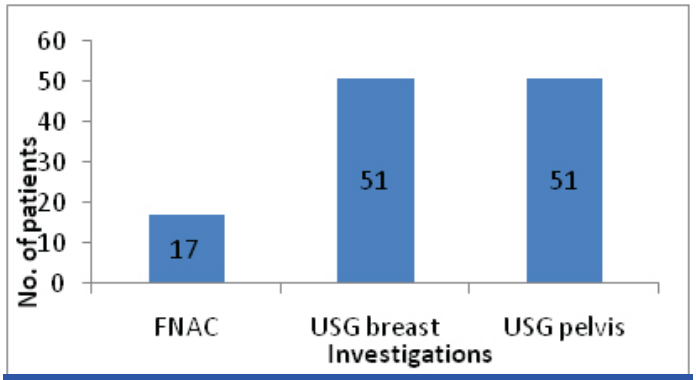
This study included 51 patients with mastalgia or fibroadenosis. In this study most of the patients were in the age group of 26-35years (70.6%) followed by age group of <25 years (15.7%) and age group of 36-45(11.8%) [Table/Fig-1].

Ultrasound breast was done for all 51 patients and Fine Needle Aspiration Cytology (FNAC) was done for 17 patients to confirm fibroadenosis/fibroadenoma and to rule out malignancy [Table/Fig-2]. Thirty patients were found to have cyclical mastalgia (58.8%) followed by fibroadenosis and fibroadenoma in 17 patients (33.4%) and four patients (7.8%) had non-cyclical mastalgia [Table/Fig-3].

Regarding side effects, epigastric pain was reported by three patients (5.9%) and ten patients (19.6%) reported menstrual delay during the course of the treatment. Thirty eight patients did not complain of any side effect [Table/Fig-4].

Age distribution in (y)	Number of patients	Percentage (%)
<25	8	15.7
26-35	36	70.6
36-45	6	11.8
46-55	1	1.9
>55	0	0
Total	51	100

[Table/Fig-1]: Age distribution of patients.



[Table/Fig-2]: Investigations.

Diagnosis	No of patients	Percentage (%)
Cyclic mastalgia	30	58.8
Non-cyclic mastalgia	4	7.8
Fibroadenoma & Fibroadenosis	17	33.4
Total	51	100

[Table/Fig-3]: Distribution of clinical presentation.

Side effects	Number of patients	Percentage (%)
Gastritis	3	5.9
Menstrual delay	10	19.6
No side effects	38	74.5
Total	51	100

[Table/Fig-4]: Distribution of side effects.

Pain score	First visit 4th week	Second visit 8th week	Third visit 12th week	Fourth visit 16th week	Fifth visit 20th week	Sixth visit 24th week
0	0	0	15	31	46	46
2	10	17	20	13	1	1
4	37	30	12	3	0	0
6	4	4	4	4	4	4
8	0	0	0	0	0	0
10	0	0	0	0	0	0
Total	51	51	51	51	51	51

[Table/Fig-5]: Distribution of VAS pain score on each visit.

	Mean±S.D	95% Confidence Interval of the Difference		p-value
		Lower limit	Upper limit	
First with second visit	0.1373±0.6639	0.495	0.3240	0.146
First with third visit	0.7843±0.8789	0.5371	1.0315	0.009*
First with fourth visit	1.2745±0.8265	1.0420	1.5070	0.001*
First with fifth visit	1.6275±0.6312	1.4499	1.8050	0.001*
First with sixth visit	1.6275±0.6312	1.4499	1.8050	0.001*

[Table/Fig-6]: Correlation between the VAS pain score on each visit.
*p value < 0.05 is statistically significant

Before starting treatment, four patients presented with VAS score for pain of 6 followed by, 37 patients with a score of 4 and 10 patients with a score of 2. Then patients were started on tab centchroman 30mg OD alternate days and were reviewed on the second visit after 4 weeks. Thirty patients have reported with pain score 4 followed by 17 patients with pain score of 2. Patients were asked to review for third visit after 8 weeks continuing treatment with Tab. Centchroman 30mg OD alternate days. This showed 20 patients have reported with pain score 2 and 15 patients with pain score of 0. During the fourth visit medication was stopped and 31 patients reported with pain score 0 and 13 patients reported with pain score of 2. On fifth and sixth visit, 46 patients reported with pain score 0, one patient with pain score of 2 and four patients with pain score of 6 [Table/Fig-5].

Four patients had reported with pain score of 6 during the treatment hence discontinued treatment and they were subjected to other modalities of treatment. The efficacy of centchroman is found to be significant (p-value = 0.001) [Table/Fig-6] after comparing the pain score on each visit.

DISCUSSION

Kaur N et al., in their study on a sample size of 262 consecutive women attending surgery OPD with complaints of mastalgia and nodularity in breasts revealed that 17% of them were proved to have BBD [9]. Of these, 36% of them had fibroadenoma and 39% were suffering from mastalgia with or without nodularity. Salzmann et al., in their study noted that 42% of women suffering from BBD had breast lumps and 66% of them had mastalgia either cyclical or non-cyclical [17]. Earlier in 2004, Smith et al., also in their study on 1171 women attending gynaecology OPD have documented that as high as 69% of them experienced some amount of pre-menstrual breast symptoms [18]. Chang et al., in their study done in 2006 with a sample size of 998 women with moderate to severe mastalgia it was found that most women had relief with oestrogen receptor modulators. Mastalgia is a common complaint with 66% of normal women experiencing at some point [19]. Horner NK et al., had inferred that half the women population with symptoms ranging from pain and nodularity due to fibrocystic breast disease is due change in internal hormonal environment [20]. An Indian study by Uma et al., on 58 cases of mastalgia revealed 57% of cyclical mastalgia and the remaining 43% experienced non - cyclical

Mastalgia, 64% of them with nodularity [21]. Another study by Khan et al., 271 cases of mastalgia inferred that prevalence of non-cyclical mastalgia being slightly higher than cyclical mastalgia [22]. Plu-Bureau G et al., and Kataria et al., have reported that cyclical mastalgia might be an independent risk factor for developing malignancy based on their finding that 22 of 247 of cyclical mastalgia cases on 16 year follow-up developed breast cancer [23,24]. Fibrocystic disease and fibroadenoma are also proved to be potential conditions for turning malignant later especially if they have undergone FNAC/trucut biopsy [25]. Janaki KL et al., in their in a community based study on 1000 women, have concluded that benign breast diseases especially mastalgia, fibroadenosis and fibroadenoma are most common than malignant ones [26]. Hence, it essential to treat these conditions with appropriate drugs and to follow them for longer period. Many drugs like gamoleinic acid [27], tamoxifen [28,29], evening primrose oil and fish oil [30], danazol [31,32], bromocriptin [33], goserelin [34], topical nonsteroidal anti-inflammatory drugs [35], diuretics, vitamins, antioxidants, oral contraceptive pills and measures like sports brassiere [36], low fat & high carbohydrate diet [37], caffeine free diet [38] and even just reassurance and periodical follow-up [39]. There is a debate on the choice of treatment of fibroadenosis and mastalgia due to varying efficacy and side effects and cost of the drugs; Centchroman is the latest addition [40]. Centchroman (Ormeloxifene-$C_{30}H_{35}NO_3$) is a non-hormonal, non-steroidal oral contraceptive pill [41]. It is a SERM or SERMs, which acts on the estrogen receptor [42,43]. Centchroman is also used as a contraceptive pill, post coital pill, as treatment for abnormal uterine bleeding anti-osteoporotic and in advanced breast cancer along with other palliative measures [41-44]. It was first formulated by Central Drug Research Institute, Lucknow, India and was included in the National Family Welfare Program in 1995 (Trade name SAHELI by Hindustan Latex Ltd. usual price Rs 2 per 30 mg tablet per day). Centchroman is free from side effects like nausea, vomiting, weight gain and dizziness; it does not delay return of fertility after stoppage and has only one side effect of delayed menses in less than 10% of cases. It has adverse effects on endocrine, haematologic, liver, cardiovascular, central nervous and lipid functions [44-46]. On review of literature only a very few studies are found on the usage of Centchroman for Mastalgia and fibroadenosis and fibroadennoma [Table/Fig-7,8]. These studies have recommended that centchroman is similar to or better than other medications because of its minimal side effects and cost effectiveness.

Our study was conducted between July 2013 to July 2015 on 51 patients with complaints of breast pain and nodularity, fulfilling inclusion and exclusion criteria. This study was carried out by us, after extensive web search we could find only four studies on usage of centchroman for treatment of mastalgia and fibroadenosis [47-52]. [Table/Fig-7,8] show the comparative data of our study with those of previous authors on effectiveness of centchroman on regression of mastalgia and fibroadenosis.

S.no	Authors	Type of study	Sample size	Age distribution	% of mastalgia / fibroadenosis
1	Dhar A et al., 2007 [47].	Non randamised study.	60	<35yrs. (100%)	70% / 30%
2	Tejwani PL et al., 2011 [48].	Randomized comparative study of the efficacy of Danazol and Centchroman on Mastalgia.	81	All in reproductive age group	100% / 0%
3	Kumar S et al., 2013 [49].	Randomized, double blind, placebo-controlled trial of Ormeloxifene in breast pain and nodularity.	151	Mean age 33.7 ± 7.45 yrs.	100% / 100%
4	Jain BK et al., 2015 [50].	Prospective randomized controlled trial to compare Tamoxifen with Centchroman (Ormeloxifene) in the management of mastalgia.	Data not available	Data not available	Data not available
5	Bansal V et al., 2015 [51].	Randomized control trial of oral ormeloxifene.	203	20-50 yrs Mean age- 32.8 ± 8.35	Data not available
6	Rathi J et al., 2016 [52].	Type of study not mentioned.	100	Data not available	Data not available
7	Present study, 2016	Prospective non randomised study.	51	26-35 yrs. (70.6%) 36-45yrs. (11.8%)	66.6% / 33.4%

[Table/Fig-7]: A comparison of other similar studies.

Serial no	Authors	Centchroman dosage	Outcome of the study		
			Regression of Mastalgia with Centchroman	Regression of fibroadenosis with Centchroman	Side effects with Centchroman
1	Dhar A et al., 2007 [47].	30 mg on alternate days for a period of 3 months and were followed up for 6 months.	There was a good response in the mastalgia group, with a decrease in the VAS scoring from 10 to 3 in 90% of the patients in the first week. Almost all of the patients were painless at the end of one month.	Complete disappearance of the nodularity. In the fibroadenoma group there was a mixed response, with complete disappearence in 40%, partial regression in 20% and no response at all in the remaining 40%.	There were very few side effects.
2	Tejwani PL et al., 2011 [48].	Centchroman 30 mg daily daily for 12 weeks and were followed for another 12 weeks.	There was significant relief of mastalgia (p=0.001).	Not applicable.	Mild menstrual irregularities – subsided after stopping the drug.
3	Kumar S et al., 2013 [49].	30 mg, twice a week for 3 months and followed up for 6 months.	The mean pain level showed a systematic downward trend over five visits (p<0.001).	Breast nodularity grades during successive visits showed significant improvement.	Oligomenorrhoea alone was reported by 12 patients.
4	Jain BK et al., 2015 [50].	30 mg daily for 12 weeks and followed up for another 12 weeks.	Gradual improvement in mastalgia with passage of time up to 12 weeks. Following cessation of treatment at 12 weeks, partial relapse of pain was observed at 24 weeks.	Not applicable.	Side effects namely dizziness, menstrual irregularities and development of ovarian cysts.

5	Bansal V et al., 2015 [51].	30 mg twice a week for 3 month and followed up for 6months.	The mean pain score was considerably decreases till three month and after three months when treatment was stopped. There was significant decrease in pain score after six month.	There was significantly greater improvement in the grade of nodularity in the third and sixth month.	There was no any major side-effect reported by patients except for oligomenorrhoea in 9 patients and 3 was with mild headache.
6	Rathi J et al., 2016 [52].	30 mg/day for 12 weeks followed by observation for 12 weeks.	The median pain score was significantly reduced over successive visits. (p = 0.001).	Not applicable.	Minimal side effects.
7	Present study, 2016	30 mg alternate days for a period of 3 months and followed up for 6 months.	Out of 51 patients, 38 patients (74.5%) had relief of symptoms without any side effects at 4th visit itself (p = 0.001).	We did not observe any case of fibroadenosis showing even partial regression. Probably longer follow-up period with longer duration therapy with higher dosage is needed.	Ten patients (19.6%) and three patients (5.9%) had side effects of menstrual delay and gastritis respectively. Menstrual irregularities were reversed to normal once the patient stopped taking medication.

[Table/Fig-8]: Outcomes of the present in comparison with previous studies.

LIMITATION

Our study is a non randomized one with a small sample size using single drug only. However, multicenrtric randomised double blind controlled studies with larger sample size in comparison with other drugs are needed for global acceptance.

CONCLUSION

From this study, we infer that centchroman is a safe and cost effective drug with significant efficacy on regression of fibroadenosis and mastalgia in the women of reproductive age group with minimal side effect. Our results are in consistent with four other studies available in the medical literature. One of the previous four studies had high frequency of side effects, particularly development of ovarian cyst with Centchroman. However, multicenrtric randomised double blind controlled studies with larger sample size in comparison with other drugs are needed for global acceptance.

ETHICS COMMITTEE APPROVAL

Institutional Human Ethical Committee (IHEC), Mahatma Gandhi Medical College & Research Institute, Pondicherry-607402. Approval reference number – PG/2014/28.

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